Chapter 5
Viral Hepatitis

A1a. Define basis for interferon resistance in humans. The NIH-funded Virahep-C study has evaluated clinical factors associated with non-response and has identified race, viral level, sex, degree of hepatic fibrosis and amount of medication taken as key clinical factors. The biologic basis remains unclear, but is the subject of ancillary studies of Virahep-C and several other NIH R01 grants. (10%)

A1b. Define efficacy of interferon and ribavirin in subgroups of HCV patients. Studies are ongoing regarding response rates and predictors of response to combination therapy of hepatitis C, including studies in children (Peds-C), liver transplant candidates (A2ALL: LADR Study), patients with renal failure (Intramural NIH; Roche), substance abusers (Sylvestre DL. *J Subs Ab Treat* 2005; 29:159), and minorities (Virahep-C; Latino Study, Roche). (20%)

A2. Fully define the pathways of interferon induction and effector action against HCV and HBV *in vitro* and *in vivo*. Multiple studies from NIH-funded investigators have demonstrated interactions between HCV and interferon signaling pathways leading to enhanced production of interferon and interferon-induced gene expression (Gale M Jr and Foy EM. *Nature* 2005;436:939). The interferon-beta promoter stimulator 1 (IPS-1) appears to be a key protein and a potential point of attack by HCV for immune evasion (Meylan E. *Nature* 2005;437:1167). Further research is needed to assess the clinical relevance of these findings in humans. (30%)

A3. Develop a cell culture system that is fully permissive for HCV replication. Three groups of NIH-funded investigators have reported a cell culture system for HCV using a full-length cDNA clone of genotype 2 HCV from a Japanese patient with severe hepatitis (Zhong J. *PNAS* 2005;102:9294; Lindenbach BD. *Science* 2005;309:623; Wakita T. *Nature Med* 2005;11:791). Further refinement of cell culture systems is needed to include all HCV genotypes and optimize culture conditions for studies of viral life cycle, neutralization and infectivity. (50%)

B1a. Fully define early events during HCV and HBV infection. Early events during HCV and HBV infection have been further characterized by NIH-funded investigations in chimpanzees (Wieland SF and Chisari FV. *J Virol* 2005;79:9369). The relevance of these findings in humans is being evaluated. The early immune responses during acute hepatitis C is a specific focus of the recently NIH-funded Hepatitis C Cooperative Research Centers Program. (20%)

B1b. Define whether long-term interferon therapy is beneficial in non-responders with HCV. Long-term peginterferon therapy is being evaluated in both NIH- (HALT-C) and industry-funded (EPIC3, Schering) studies. Results will be available in 2-3 years. (0%)

B2a. Identify new targets in viral replication and the host for development of small molecule therapeutics (HCV, HBV, HDV). NIH investigators have identified new targets in viral replication for HBV (receptor blockers, fatty acid biosynthetic pathways), HCV (inhibitors of membrane association, calcineurin

inhibitors, mediators of lipid metabolism), and HDV (prenylation inhibitors). None of these molecules have been tested in humans. (0%)

B2b. Define the molecular basis for antiviral resistance of HBV. Antiviral resistance of HBV has been studied largely by industry-sponsored scientists focusing upon proprietary nucleoside analogs. Prospective studies of humans that would include analysis of antiviral resistance have been proposed. (0%)

B3a. Develop small animal models of HCV replication and liver disease. Current animal models are limited in availability and applicability, but this need is likely to diminish if recently described cell culture systems fulfill their initial promise. NIH initiatives include a contract for *in vitro* and *in vivo* models of HCV infection (AI-25488), and an RFP (AI-05-012) and PA for animal models (DK-05-049). (10%)

B3b. Better characterize the HBV life cycle, virus-host interactions, basis for generation and stability of cccDNA and viral state of HBV in humans. HBV life cycle is the focus of several investigator-initiated NIH grants. An NIH workshop on HBV is scheduled for April 2006. (0%)

C1a. Evaluate new approaches to therapy in all five forms of viral hepatitis. NIH-funded investigators and several biotechnology companies are investigating the potential of RNA silencing (RNAi) as antiviral therapy for hepatitis C and B (Uprichard SL. *PNAS* 2005;102:773; Morrissey D. *Nat Biotech* 2005;23:1002). New approaches have yet to be initiated in humans. (10%)

C1b. Evaluate long-term benefits and risks of combination therapy of HBV. The long-term benefits and risks of combination therapy of HBV are being evaluated in NIH intramural studies, and prospective studies have been proposed. In the short-term, combination therapy (adefovir and lamivudine; peginterferon and lamivudine) does not appear to be better than monotherapy. An NIH workshop on management of HBV is scheduled for April 2006. (10%)

C2a. Develop ways to prevent re-infection after liver transplant for HCV (e.g. HCIG, anti-virals). A trial of therapy of hepatitis C before transplantation has been initiated (A2ALL, LADR Study: NIH and Schering). Pilot studies of HCIG by NIH-funded investigators and a Canadian group have failed to show significant benefit. Monoclonal antibodies to E2 glycoprotein have been shown to have neutralizing activity and may have potential in the transplant situation (Schofield DJ. *Hepatology* 2005;42:1055). (10%)

C2b. Achieve sustained response rate of over 90 percent in chronic hepatitis C. The sustained virological response rate to current therapy (peginterferon plus ribavirin) is 50-60 percent, and is higher in patients with genotypes 2 and 3 (approximately 80 percent) than genotype 1 (approximately 45 percent). Recently, two approaches have promised higher response rates: (1) high doses of ribavirin with peginterferon (Lindahl K. *Hepatology* 2005;41:275) and (2) novel protease and polymerase inhibitors with and without peginterferon in several phase II, industry-funded trials. (0%)

C3a. Develop HCV vaccine. An HCV vaccine has been developed by Chiron Corporation and evaluated in phase I trials largely in NIH-sponsored Vaccine and Treatment Evaluation Units. Phase II-III trials are being designed. HCV vaccine

development is an active area of individual investigator, NIH-funded research (10%)

C3b. Develop therapeutic HBV vaccine. NIH-funded basic research on innate immunity and T cell responses to vaccines promises to provide impetus to further work on a therapeutic HBV vaccine. The development of a therapeutic vaccine is being pursued using the transgenic mouse model of HBV infection. (0%)

Figure 7. Estimated Progress on Viral Hepatitis Research Goals, 2005 (Year 1)